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(71) Applicant (for all designated States except US): UNIVER-
SITEIT LEIDEN [NL/NL]; Stationsweg 46, NL-2312 AV
Leiden (NL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CHANG, Lisa**,
C., W. [—/NL]; NL- (NL). **IJZERMAN, Adriaan**, P.
[—/NL]; NL- (NL). **BRUSSEE, Johannes** [—/NL]; NL-
(NL).

(74) Agent: **WINCKELS, J., H., F.**; Verenigde, Johan de Wit-
tlaan 7, NL-2517 JR Den Haag (NL).

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(54) Title: PYRIMIDINES DERIVATIVES AS ADENOSINE RECEPTORS LIGANDS

(57) Abstract: Use of a compound of formula (I) wherein R and R' are selected from hydrogen, alkyl, alkenyl, alkynyl, or aryl; R'' and R''' are selected from hydrogen, acyl, thio-acyl, seleno-acyl, alkyl, alkenyl, alkynyl, or aryl; or a pharmaceutically acceptable salt thereof to interact with the adenosine receptors in the beneficial treatment or prevention of a (dis)order arising from the said receptors. The invention also provides pharmaceutical compositions comprising a compound according to the present invention. The invention further relates to the use of said compositions to treat and/or prevent a variety of diseases.

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Title: PYRIMIDINES DERIVATIVES AS ADENOSINE RECEPTORS LIGANDS

FIELD OF INVENTION

The present invention relates to a particular novel category of 2,4,6-trisubstituted pyrimidines, pharmaceutical compositions containing them and the use of said compounds and compositions.

5

BACKGROUND OF THE INVENTION

The endogenous neuromodulator adenosine acts extracellularly via activation of specific membrane-bound receptors called P1-purinoceptors. These adenosine receptors are divided into four subclasses, A₁, A_{2A}, A_{2B} and A₃ receptors. All four classes are coupled to the enzyme adenylyate cyclase. Activation of the adenosine A₁ and A₃ receptors can lead to an inhibition of adenylyate cyclase, while activated A_{2A} and A_{2B} receptors can stimulate adenylyate cyclase. The adenosine receptors are ubiquitously distributed throughout the body, and can modulate diverse physiological functions, including induction of sedation, relaxation of smooth muscle and vasodilation. Activation of these receptors by adenosine can therefore be of importance in many disease states. Accordingly, blocking these receptors can produce an effect leading to the prevention or treatment of many diseases. For example, the A_{2A} adenosine receptor antagonists are reported to have a beneficial effect on neurodegenerative diseases such as Parkinson's disease.¹

20 In recent years, a number of new and interesting ligands which block the various adenosine receptor subtypes have been synthesised. These ligands encompass bi- and tri-cyclic heteroaromatic systems - featuring 3-nitrogen tri-cyclic systems (e.g., the imidazoquinolines);² 4-nitrogen tri-cyclic systems (e.g., triazoloquinoxalines);³ 6-nitrogen tri-cyclic systems (e.g., the pyrazolotriazolopyrimidines);⁴ 2-nitrogen bi-cyclic systems (e.g., the naphthyridines);⁵ and 3-nitrogen bi-cyclic systems (e.g., deazaadenines).⁶

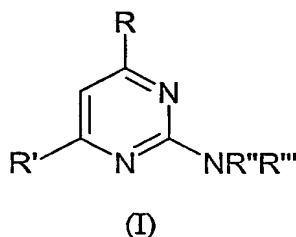
SUMMARY OF THE INVENTION

It has now been found that a particular novel category of 2,4,6-trisubstituted pyrimidines can very attractively be used to treat adenosine receptor mediated conditions.

5

Accordingly, the present invention relates to a compound of the general formula (I):

10



15 or a salt thereof,
wherein

R represents hydrogen (except when R' = H), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl;

R' represents hydrogen (except where R = H), (substituted) alkyl, (substituted) 20 alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl;

R'' represents hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl;

R''' represents hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl;

25 R'' and R''' can also together form a substituted or unsubstituted heterocyclic ring or heterocyclic rings; and n is a number in the range of from 0 to 10.

The compounds in accordance of the present invention block various adenosine receptor sybtypes, thus establishing that diseases such as amongst

others cardiovascular, neurological, and immunological disorders can very attractively be treated and/or prevented.

In the context of the present invention the term '*adenosine receptor mediated conditions*' is intended to include disease states or conditions characterised by their responsiveness to treatment with an adenosine receptor mediating compound, e.g. a 2,4,6-trisubstituted pyrimidine derivative as described by general formula (I), where the treatment causes a significant diminishment of at least one symptom or effect of the state achieved with an adenosine receptor mediating compound of the invention.

In the context of the present invention by the term '*alkyl*' it is meant any saturated hydrocarbon, either branched or unbranched comprising from 1 to about 30 carbon atoms. This includes straight-chained alkyl groups, branched-chained alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups. This term further includes alkyl groups, which can further include oxygen, nitrogen, sulphur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In preferred embodiments, a straight or branched chain has 30 or less carbon atoms in its backbone, and more preferably 20-carbon atoms or less. Likewise, preferred cycloalkyls have from 3-10 carbons, and more preferably 3-7 carbons in the ring-structure.

In the context of the present invention the terms '*acyl*', '*thio-acyl*' and '*seleno-acyl*' refer to compounds of the kind '*C(O)X*', '*C(S)X*', and '*C(Se)X*', respectively, where *X* in turn represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl.

In the context of the present invention the term ' $-(CH_2)_n$ -aryl' means a short straight alkyl chain between the (substituted) aryl group and the drawn structure, where *n* can range of from 0 up to and including 10.

In the context of the present invention the term '*aryl*' as used herein, refers to aromatic groups which can include 5- and 6- membered single-ring groups, with 0 to 4 heteroatoms, for example benzene, pyrrole, furan, thiophene, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. The aryl groups can suitably include polycyclic fused aromatic groups such as naphthyl, quinolyl, indolyl, benzoxazole, benzothiazole and the like. Those aryl groups containing heteroatoms may also be referred to as heteroaryls or heteroaromatics. The aromatic ring may be substituted at one or more ring positions, with such substituents as described herein. Aryl groups can also be fused or bridged with alicyclic or heteroalicyclic rings which are not aromatic.

In the context of the present invention the term '*substituted*' is intended to include substituents replacing hydrogen on one or more of the carbons of a moiety. Such substituents suitably include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkyl carbonyl, alkyloxy carbonyl, amino carbonyl, alkylthiocarbonyl, alkyoxyl, phosphate, phosphonate, phosphinato, cyano, amino (including alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino), acylamino, (including alkylcarbonylamino, arylcarbonylamino, carbamyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. It will be understood to those skilled in the art that the moieties substituted on the (unsaturated and saturated) carbon chain can themselves be substituted, if appropriate.

In the context of the present invention the term '*heteroatom*' refers to an atom of any element other than carbon or hydrogen. Preferred heteroatoms are oxygen, nitrogen, sulphur and phosphorus.

5 In the context of the present invention the terms '*alkenyl*' and '*alkynyl*' refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

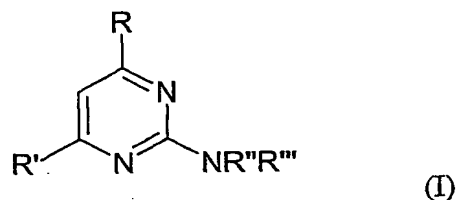
10 In the context of the present invention *salts* of the compound of the present invention are meant to include any physiologically acceptable salt. The term '*physiologically acceptable salt*' refers to any non-toxic alkali metal, alkaline earth metal, and ammonium salts commonly used in the pharmaceutical industry, including the sodium, potassium, lithium, calcium, 15 magnesium, barium ammonium and protamine zinc salts, which can be prepared by methods known in the art. The term also includes non-toxic *acid addition salts*, which are generally prepared by reacting the compounds of the present invention with a suitable organic or inorganic acid. The acid addition salts are those which retain the biological effectiveness and properties 20 of the free bases and which are not biologically or otherwise undesirable. Examples include those derived from mineral acids, and include, *inter alia*, hydrochloride, hydrobromic, sulphuric, nitric phosphoric, metaphosphoric and the like. Organic acids include, *inter alia*, tartaric, acetic, propionic, citric, malic, malonic, lactic, fumaric, benzoic, cinnamic, mandelic, glycolic, gluconic, 25 pyruvic, succinic, salicylic and arylsulfonic, e.g. p-toluenesulfonic, acids. According to one embodiment of the invention, the substituent R represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl; R' represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl; R'' 30 represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl,

(substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl; R''' represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) or $-(CH_2)_n$ -aryl; and R'' and R''' can also together form a substituted or unsubstituted heterocyclic ring or heterocyclic rings.

5

In a preferred embodiment, the present invention relates to a pharmaceutical composition comprising as active ingredient one or more compounds of the general formula (I):

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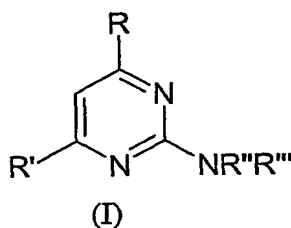
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or a salt of said compound(s), wherein R , R' , R'' , R''' have the meaning as defined hereinbefore.

DETAILED DESCRIPTION OF THE INVENTION

The present invention further relates to compounds of the general formula (I):

20



or a salt thereof,

25

wherein

R represents hydrogen (except when $R' = H$), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl;

R' represents hydrogen (except where $R = H$), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) $-(CH_2)_n$ -aryl;

- R'' represents hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) $-(CH_2)_n$ -aryl;
R''' represents hydrogen, acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) $-(CH_2)_n$ -aryl;
5 R'' and R''' can also together form a substituted or unsubstituted heterocyclic ring or heterocyclic rings; and n is a number in the range of from 0 to 10.

- More particularly, the present invention relates to compounds of general formula (I) or salts thereof, wherein R represents a hydrogen (except
10 when R' = H), alkyl, or (substituted) $-(CH_2)_n$ -aryl;
R' represents a hydrogen (except when R' = H), alkyl, or (substituted) $-(CH_2)_n$ -aryl;
R'' represents a hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl, or (substituted) $-(CH_2)_n$ -aryl;
15 R''' represents a hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl, or (substituted) $-(CH_2)_n$ -aryl; and R'' and R''' can also together form a substituted or unsubstituted heterocyclic ring or heterocyclic rings.

- According to another preferred embodiment of the present invention,
20 R represents a (substituted) $-(CH_2)_n$ -aryl; R' represents a (substituted) $-(CH_2)_n$ -aryl; R'' represents a hydrogen, methyl; and R''' represents an acyl, thio-acyl, seleno-acyl.

- Preferably, R represents a (substituted) $-(CH_2)_n$ -aryl; R' represents a
25 (substituted) $-(CH_2)_n$ -aryl; R'' represents an acyl, thio-acyl, seleno-acyl; and R''' represents a hydrogen, methyl.

- In a more preferred embodiment, R represents a phenyl; R'
represents a phenyl; R'' represents a hydrogen, methyl; and R''' represents an
30 acyl.

In another preferred embodiment, R represents a phenyl; R' represents a phenyl; R'' represents an acyl; and R''' represents a hydrogen or methyl.

5

In yet another preferred embodiment, R represents a (substituted) alkyl; R' presents a (substituted) alkyl; R'' represents a hydrogen or methyl; and R''' represents an acyl.

10

In another preferred embodiment, R represents a (substituted) alkyl; R' represents a (substituted) alkyl; R'' represents an acyl, thio-acyl or seleno-acyl; and R''' represents a hydrogen or methyl.

15

Preferably, the compound is chosen from the group consisting of N-(4,6-diphenyl-pyrimidin-2-yl)-benzamide, N-(4,6-diphenyl-pyrimidin-2-yl)-formamide, N-(4,6-diphenyl-pyrimidin-2-yl)-propionamide, N-(4,6-diphenyl-pyrimidin-2-yl)-butyramide, pentanoic acid (4,6-diphenyl-pyrimidin-2-yl)-amide, N-(4,6-diphenyl-pyrimidin-2-yl)-isobutyramide, N-(4,6-diphenyl-pyrimidin-2-yl)-2,2-dimethyl-propionamide, N-(4,6-diphenyl-pyrimidin-2-yl)-3-methylbutyramide, N-(4,6-diphenyl-pyrimidin-2-yl)-2-ethyl-butyramide, cyclopropane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide, cyclobutane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide, cyclopentane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide, cyclohexanecarboxylic acid-(4,6-diphenyl-pyrimidin-2-yl)-amide or a salt thereof.

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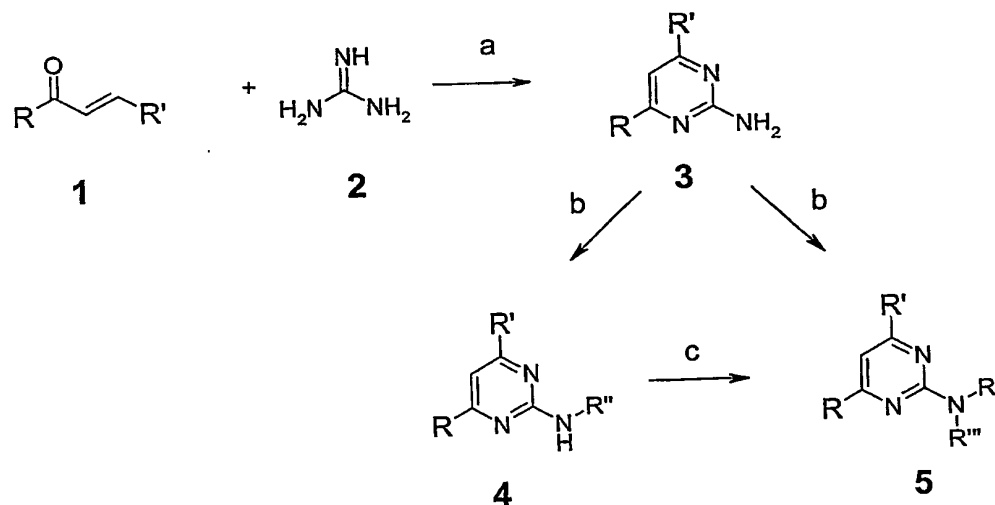
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More preferably, the compound is chosen from the group consisting of N-(4,6-diphenyl-pyrimidin-2-yl)-formamide, N-(4,6-diphenyl-pyrimidin-2-yl)-propionamide, N-(4,6-diphenyl-pyrimidin-2-yl)-butyramide, pentanoic acid (4,6-diphenyl-pyrimidin-2-yl)-amide, , N-(4,6-diphenyl-pyrimidin-2-yl)-isobutyramide, N-(4,6-diphenyl-pyrimidin-2-yl)-2,2-dimethyl-propionamide, N-

30

(4,6-diphenyl-pyrimidin-2-yl)-3-methylbutyramide, N-(4,6-diphenyl-pyrimidin-2-yl)-2-ethyl-butyramide, cyclopentane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide.

- 5 Most preferably, the compound comprises N-(4,6-diphenyl-pyrimidin-2-yl)-formamide, N-(4,6-diphenyl-pyrimidin-2-yl)-butyramide, N-(4,6-diphenyl-pyrimidin-2-yl)-3-methylbutyramide, or cyclopentane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide.
- 10 The compounds of the present invention may be prepared by several synthetic procedures. For example, the synthesis route to obtain some 2,4,6-trisubstituted derivatives is depicted in the scheme herein below:



- 15 **Scheme 1:** (a) NaOH, H₂O, EtOH; (b) carboxylic acid derivative, base, coupling agent; or an aldehyde, NaH(BOAc)₃; or a hydrocarbon halide, base.

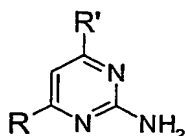
According to this scheme, the synthesis started with reacting a chalcone with a guanidine in the presence of sodium hydroxide to yield the primary amine (3).⁷ Direct reaction with an acid chloride in the presence of a base such as triethylamine gave an acyl group (4). This product could also be achieved

20

using a carboxylic acid and a standard coupling agent such as EDC in the presence of HOBT and base. When compound (3) was reacted with an aldehyde or an alkyl iodide, singly (4) or doubly substituted compounds (where $R'' = R'''$) (5) were made, respectively. The singly substituted compound (4) was further
5 reacted with another aldehyde or alkyl iodide to give compound (5) where R'' differed from R''' .

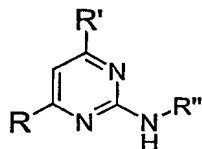
The present invention also relates to a process for preparing a compound according to the present invention, which process comprises the steps of:

- (a) reacting a compound having the structure $\text{RCOCHCHR}'$ with guanidine,
10 or a salt thereof, to form a product having the structure



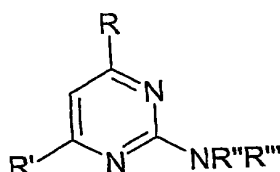
wherein R represents hydrogen (except when $R' = \text{H}$), (substituted) alkyl, substituted alkenyl, (substituted) alkynyl or (substituted) $-(\text{CH}_2)_n\text{-aryl}$; R'
15 represents hydrogen (except when $R = \text{H}$), (substituted) alkyl, substituted alkenyl, (substituted) alkynyl or (substituted) $-(\text{CH}_2)_n\text{-aryl}$; and is a number in the range of from 0 to 10;;

- (b) reacting the product formed in step (a) with a compound having the structure of R'' aldehyde, R'' halide or R'' carboxylic acid or a derivative thereof,
20 to form a product having the structure



wherein R" represents (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl or (substituted) $-(CH_2)_n$ -aryl, wherein n has the meaning as defined hereinbefore; and

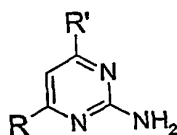
- (c) reacting the product formed in step (b) with a compound having the structure of R"aldehyde, R"halide or R"carboxylic acid or a derivative thereof,
 5 to form a product having the structure



- wherein R''' represents acyl, (substituted) alkyl, (substituted) alkenyl,
 10 (substituted) alkynyl or (substituted) $-(CH_2)_n$ -aryl, and wherein n has the meaning as defined hereinbefore.

The present invention also relates to a process for preparing a compound according to the present invention, which process comprises the steps of:

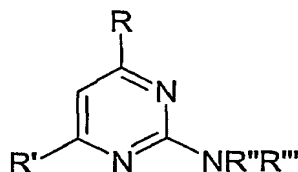
- 15 (a) reacting a compound having the structure $RCOCHCHR'$ with guanidine, or a salt thereof, to form a product having the structure



- 20 wherein R represents hydrogen (except when R' = H), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl or (substituted) $-(CH_2)_n$ -aryl; R' represents hydrogen (except when R = H), (substituted) alkyl, substituted)

alkenyl, (substituted) alkynyl or (substituted) $-(CH_2)_n$ -aryl; and n is a number in the range of from 0 to 10.;

- (b) reacting the product formed in step (a) with a compound having the structure of R'' aldehyde, R'' halide or R'' carboxylic acid or a derivative thereof,
 5 to form a product having the structure



- R'' represents acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl; R''' represents acyl, (substituted) alkyl,
 10 (substituted) alkenyl, (substituted) alkynyl or (substituted) $-(CH_2)_n$ -aryl; and n has the meaning as defined herein before.

Suitably, steps a and b can be carried out at temperatures ranging from ambient to 300 °C.

- Derivatives of the carboxylic acid can be, but are not exclusively,
 15 carboxylic acid chlorides, carboxylic acid fluorides, carboxylic acid anhydrides or esters.

In a preferred embodiment, the present process comprises the steps of:

- 20 (a) reacting a compound having the structure of benzylidenacetophenone (chalcone) with guanidine having the structure to form a product having the structure of a 4,6-diphenyl-2-aminopyrimidine,
 (b) reacting the product formed in step (a) with a carboxylic acid or a carboxylic acid derivative to form a product having the structure of a 4,6-
 25 diphenyl-2-amidopyrimidine.

In a more preferred embodiment, the present process comprises the steps of:

- (a) reacting a compound having the structure of benzylidenacetophenone (chalcone) with guanidine having the structure to form a product having the structure of a 4,6-diphenyl-2-aminopyrimidine;
- (b) reacting the product formed in step (a) with a carboxylic acid or a carboxylic acid derivative to form a product having the structure of a 4,6-diphenyl-2-amidopyrimidine;
- (c) reacting the product formed in step (b) with butyryl chloride to form a product having the structure of N-(4,6-Diphenyl-pyrimidin-2-yl)-butyramide.

The present invention also relates to a pharmaceutical composition comprising as active ingredient one or more compounds according to the present invention. The compound according to the present invention can be used as such. However, also a salt or a solvate of the compound may be used. It will be understood that such salt or solvate should be pharmaceutically acceptable. The skilled person will further understand that the pharmaceutical composition will also comprise a suitable pharmaceutical carrier.

The present invention further relates to the use of a compound according to the present invention for treating and/or preventing a disorder in which the adenosine receptors are involved.

The present invention also relates to the use of a compound according to the present invention for the manufacture of a medicament for the treatment and/or prevention of a disorder in which the adenosine receptors are involved.

In addition, the present invention relates to a method for treating and/or preventing a disorder in which the interaction with the adenosine

receptors is beneficial, which method comprises administering to a subject in need of such treatment an effective dose of a pharmaceutical composition in accordance with the present invention.

5 Suitably, the disorder can be chosen from the group of diseases consisting of amongst others cardiovascular, neurological, immunological disorders, cancers and infection conditions. The compounds according to the present invention are particularly effective for treating and/or preventing kidney, heart and central nervous system (CNS) afflictions.

10 As will be detailed in Table 2, the compounds of the present invention are *biologically active*.

 The term '*biologically active*' indicates that the compound of the present invention has some sort of a biological activity, for example, a measurable effect on a target receptor. As will be detailed hereinafter, the compound of the present invention may block the biological action of adenosine receptors, thus acting as adenosine receptor antagonists.

20 The term '*antagonist*' used herein refers to a molecule that binds to a receptor without activating the receptor. It competes with the endogenous ligand for this binding site and, thus reduces the ability of the endogenous ligand to stimulate the receptor.

25 In the pharmaceutical composition according to the present invention the active ingredient will be present in an effective amount. The term '*effective amount*' for the purposes described herein is that determined by such considerations as are known to those versed in the art. The amount

must be sufficient to achieve a desired therapeutic effect, e.g. to treat a disease or disorder.

The terms '*treat*', '*treating*' and '*treatment*' refer to the
5 administering of a therapeutic amount of the compound or pharmaceutical
composition of the present invention which is effective to ameliorate undesired
symptoms associated with a disease, to prevent the manifestation of such
symptoms before they occur, to slow down the progression of a disease, to slow
down the deterioration of symptoms, to slow down the irreversible damage
10 caused by the chronic stage of a disease, to lessen the severity of, or cure a
disease, to improve survival rate or more rapid recovery, to prevent the disease
from occurring, or a combination of two or more of the above.

The terms '*modulate*', '*modulation*', and '*modulation*' are
15 intended to include preventing, eradicating, or inhibiting the resulting
increase of undesired physiological activity associated with the stimulation of
an adenosine receptor, e.g. in the context of the therapeutic methods of this
invention. In another embodiment, the term '*modulate*' includes antagonistic
effects, e.g. diminishment of the activity or production of mediators which
20 result from the (over)-stimulation of adenosine receptor(s).

The disease is preferably associated with the biological action of one
or more adenosine receptors wherein the compound of the present invention
acts as an adenosine receptor antagonist. For example antagonists of A₁
25 receptors have been implicated as compounds which may be used in the
treatment of cardiac, renal and sleep disorders.

The pharmaceutical composition of the present invention may further
comprise *pharmaceutically acceptable additives*.

Further, the term '*pharmaceutically acceptable additives*' used herein refers to any substance combined with said compound and include, without being limited thereto, diluents, excipients, carriers, solid or liquid fillers or encapsulating materials which are typically added to formulations to give
5 them a form or consistency when it is given in a specific form, e.g. in tablet form, as a simple syrup, aromatic powder, and other various elixirs. The additives may also be substances for providing the formulation with stability, sterility and isotonicity (e.g. antimicrobial preservatives, antioxidants, chelating agents and buffers), for preventing the action of microorganisms (e.g.
10 antimicrobial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid and the like) or for providing the formulation with an edible flavour, etc.

Preferably, the additives are inert, non-toxic materials, which do not react with the active ingredient of the invention. Yet, the additives may be
15 designed to enhance the binding of the agent to its receptor. Further, the term *additive* may also include adjuvants, which, by definition, are substances affecting the action of the active ingredient in a predictable way. The additive can be any of those conventionally used and are only limited by chemico-physical considerations, such as solubility and lack of reactivity with the
20 compound of the invention, and by route of administration. The active agent of the invention may be administered orally to the patient. Conventional methods such as administering the compound/s in tablets, suspensions, emulsions, capsules, powders, syrups and the like are usable. For oral administration, the composition of the invention may contain additives for facilitating oral delivery
25 of the compound/s of the invention. Formulations suitable for oral administration can consist of

- (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice;
- (b) capsules, sachets, tablets, lozenges, and troches, each containing a
30 predetermined amount of the active ingredient, as solids or granules;

- (c) powders;
- (d) suspensions in an appropriate liquid; and
- (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatine type containing, for example surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatine, guar gum, colloidal silicon dioxide, croscarmellose sodium talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active agent in a flavour, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatine and glycerine, or sucrose and acacia, emulsions, gels, and the like. Such additives are as such known in the art.

Alternatively, the compound/s may be administered to the patient parenterally. In this case, the composition will generally be formulated in a unit dosage injectable form (solution, suspension, emulsion). Pharmaceutical formulation suitable for injection may include sterile aqueous solutions or dispersions and sterile powders for reconstitution into sterile injectable solutions or dispersions. The carrier can be a solvent or dispersing medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, lipid polyethylene glycol and the like), suitable mixtures thereof and vegetable oils.

Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Non-aqueous vehicles such as

cottonseed oil, sesame oil, olive oil, soybean oil, corn oil, sunflower oil, or peanut oil and ester, such as isopropyl myristate, may also be used as solvent systems for the composition of the present invention.

Suitable fatty acids for the use in parenteral formulations include oleic acid, 5 stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

Suitable detergents for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include

- (a) cationic detergents such as, for example, dimethyl dialkyl ammonium 10 halides, and alkyl pyridinium halides,
- (b) anionic detergents such as, for example, alkyl, aryl, and olefinic sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates,
- (c) non-ionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxy-ethylenepolypropylene copolymers,`
- 15 (d) amphoteric detergents such as, for example, alkyl- β -aminopropionates, and 2-alkyl-imidazoline quarternary ammonium salts, and mixtures thereof.

Further, in order to minimise or eliminate irritation at the site of injection, the compositions may contain one or more non-ionic surfactants having a hydrophile-lipophile balance (HLB) from about 12 to about 17. 20 Suitable surfactants include polyethylenesorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The choice of an additive will be determined in part by the particular 25 compound of the present invention, as well as by the particular method used to administer the composition.

Notwithstanding the above, the composition of the present invention may include one or more of the compounds of the present invention and may compromise other biologically active substances, to provide a combined 30 therapeutic effect.

The compounds and compositions of the present invention as set forth hereinabove and below are administered and dosed in accordance with good medical practice, taking into account the clinical conditions of the individual patient, the site and method of administration, scheduling of administration, individual's age, sex, body weight and other factors known to medical practitioners.

The dose may be single doses or multiple doses over a period of several days. The treatment generally has a length proportional to the length of the disease process and drug effectiveness and the individual species being treated. Suitable doses and dosage regimens can be determined by conventional range-finding techniques known to those of ordinary skill in the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments, until the optimum effect under the circumstances is reached. Exemplary dosages range from about 0.01mg/kg body weight to about 10 mg/kg body weight of the subject being treated per day.

The invention has been described in an illustrative manner, and it is to be understood that the terminology which has been used, is intended to be in the nature of words of description rather than of limitation. Obviously, many modifications and variations of the present invention are possible in light of the above teaching. It is therefore, to be understood that within the scope of the appended claims, the invention may be practised otherwise than as specifically described hereinafter.

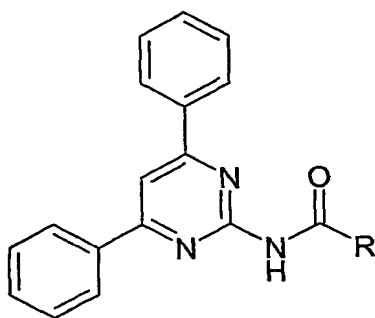
Throughout this application various publications are referred to by a number. Full citations for the publications are listed hereinafter. The disclosure of these publications in their entireties is hereby incorporated by reference into the application in order to more fully describe the state of the art to which this invention pertains.

SPECIFIC EXAMPLES – 4,6-Diphenyl-2-carboxyamidopyrimidines

This invention is further described in the following specific examples, which do not limit the scope of the invention described in the claims.

5

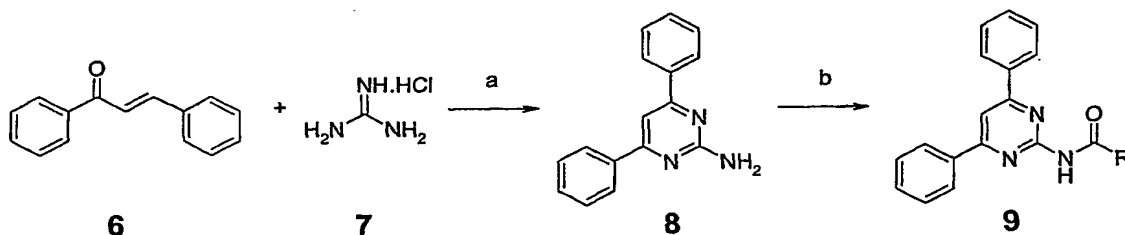
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(II)

The examples detailed here of the general formula (II) are synthesised according to the route detailed below in Scheme 2.

15



Scheme 2: (a) NaOH, H₂O, EtOH; (b) RC(O)Cl, Et₃N, 1,4-dioxane.

Chemistry – General

20

Chemicals and Solvents All reagents were obtained from commercial sources and all solvents were of an analytical grade.

Chromatography Thin-layer chromatography (TLC) was carried out using

25

Merck silica gel plastic backed F₂₅₄ plates, visualised under UV (254 nm).

Instruments and Analysis Elemental analyses were performed for C,H,N (Leiden Institute of Chemistry, Leiden University, The Netherlands). ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (^1H NMR, 200MHz; ^{13}C NMR, 50.29 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm (δ) relative to this. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Mass Spectra were measured on a Finnigan MAT TSQ-70 spectrometer equipped with an electrospray interface for ESI experiments. Spectra were collected by constant infusion of the analyte dissolved in methanol. ESI is a soft ionisation technique resulting in protonated, sodiated species in positive ionisation mode and deprotonated species in the negative ionisation mode.

Synthetic Procedures

15 2-Amino-4,6-diphenylpyrimidine (8).⁷

A mixture benzylidenacetophenone (38.6 g, 0.185 mol, 1.1 eq.) and guanidine hydrochloride (16 g, 0.168 mol, 1 eq.) were refluxed in ethanol (150 mL). Sodium hydroxide (21.6 g, 0.539 mol, 3.2 eq.) was dissolved in a minimum amount of water (40mL), and added dropwise to the refluxing mixture. The reaction mixture was then stirred at reflux for a further 6 h. Upon cooling, the reaction mixture was concentrated and then separated between ethyl acetate (200 mL) and water (200 mL). The aqueous layer was then extracted with ethyl acetate (2×100 mL). The combined organics were washed with water (200 mL) and brine (200 mL), dried over MgSO_4 , and concentrated *in vacuo*. The crude product was then purified by column chromatography on SiO_2 , eluting with dichloromethane. Recrystallisation from ethyl acetate gave clear colourless crystals yield 31%; ^1H NMR δ (CDCl_3): 8.09-8.04 (m, 4H, Ar), 7.54-7.48 (m, 7H, Ar), 5.25 (br s, 2H, NH_2).

General Procedure for the Preparation of 2-Amidopyrimidines (9-17)

To a solution of 2-amino-4,6-diphenylpyrimidine (0.202 mmol, 1 eq.) in 1,4-dioxane (5mL) was added triethylamine (0.223 mmol, 1.1 eq.), followed by the appropriate acid chloride (0.304 mmol, 1.5 eq.). This was then stirred at reflux
5 until no starting material was visible by TLC. Upon completion, the reaction mixture was separated between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was further extracted with ethyl acetate (2 × 20 mL) and the combined organics washed with water and brine. After drying over MgSO₄ and evaporation under reduced pressure, the crude product was purified by column
10 chromatography, eluting with a petroleum ether-ethyl acetate or a dichloromethane-methanol solvent system. Recrystallisation with ethanol or petroleum ether-ethyl acetate gave the corresponding amide in crystalline form.

15 **N-(4,6-Diphenyl-pyrimidin-2-yl)-benzamide (9)**. Yield 34%; white solid; mp 169-170 °C; ¹H NMR δ (CDCl₃): 8.75 (br s, 1H, N-H), 8.22-8.17 (m, 4H, ar), 8.02-7.98 (m, 2H, ar), 7.90 (s, 1H, pyrimidine-H), 7.56-7.52 (m, 9H, ar) ppm. ¹³C NMR δ (CDCl₃): 166.1, 136.5, 132.1, 131.0, 128.9, 128.7, 127.2, 108.1 ppm. MS (ES⁺): 351.50 Da. Anal. (C₂₃H₁₇N₃O) C, H, N.

20 **N-(4,6-Diphenyl-pyrimidin-2-yl)-propionamide (10)**. Yield 21%; white solid; mp 165 °C; ¹H NMR δ (CDCl₃): 8.17-8.08 (m, 5H, ar + NH), 7.81 (s, 1H, pyrimidinyl-H), 7.56-7.50 (m, 6H, ar), 3.05 (q, 2H, J = 7.30 Hz, CH₂CH₃), 1.32 (t, 3H, J = 7.31 Hz, CH₂CH₃) ppm. ¹³C NMR δ (CDCl₃): 174.8, 157.7, 136.5, 131.0, 128.8, 127.0, 107.2, 30.7, 11.5 ppm. MS (ES⁺): 303.86 Da. Anal (C₁₉H₁₇N₃O.0.2H₂O) C, H, N.

N-(4,6-Diphenyl-pyrimidin-2-yl)-butyramide (11). Yield 47%; white solid;
30 mp 157 °C; ¹H NMR δ (CDCl₃): 8.16-8.09 (m, 4H, ar), 8.08 (br s, 1H, NH),

7.83 (s, 1H, pyrimidinyl-*H*), 7.55-7.52 (m, 6H, ar),
3.02 (t, 2H, $J = 7.30$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.86 (sextet, 2H, $J = 7.30$ Hz, CH_2CH_2
 CH_3), 1.08 (t, 3H, $J = 7.30$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$)ppm. ^{13}C NMR δ (CDCl_3): 174.2,
166.0, 157.7, 131.0, 128.8, 127.1, 107.3, 39.3, 18.3, 11.8ppm. MS (ES^+): 317.95
5 Da. HRMS: 318.16 Da. Elemental analysis not performed due to insufficient
sample.

Pentanoic acid (4,6-diphenyl-pyrimidin-2-yl)-amide (12). Yield 32%;
white solid;
10 mp 157 °C; ^1H NMR δ (CDCl_3): 8.16-8.11 (m, 4H, ar), 8.09 (br s, 1H, *NH*),
7.82 (s, 1H, pyrimidinyl-*H*), 7.56-7.52 (m, 6H, ar),
3.05 (t, 2H, $J = 7.67$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.86-1.74 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$),
1.58-1.40 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.99 (t, 3H, $J = 7.30$ Hz,
 $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)ppm.
15 ^{13}C NMR δ (CDCl_3): 165.9, 157.8, 136.6, 131.0, 128.8, 127.1, 121.3, 113.6,
107.2, 37.2, 22.4, 11.8ppm. MS (ES^+): 331.86 Da. Anal. ($\text{C}_{21}\text{H}_{21}\text{N}_3\text{O} \cdot 0.2\text{H}_2\text{O}$) C,
H, N.

N-(4,6-Diphenyl-pyrimidin-2-yl)-isobutyramide (13). Yield 39%; white
20 solid;
mp 160-161 °C; ^1H NMR δ (CDCl_3): 8.17-8.10 (m, 4H, ar), 8.09 (br s, 1H, *NH*),
7.84 (s, 1H, pyrimidinyl-*H*), 7.56-7.51 (m, 6H, ar), 3.41-3.38 (m, 1H, $\text{CH}(\text{CH}_3)_2$),
1.35 (d, 6H, $J = 6.94$ Hz, $\text{CH}(\text{CH}_3)_2$)ppm. ^{13}C NMR δ (CDCl_3): 166.0, 157.7,
136.6, 136.0, 131.0, 128.8, 127.1, 107.5, 35.2, 19.2ppm. MS (ES^+): 317.94 Da.
25 Anal ($\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}$) C, H, N.

N-(4,6-diphenyl-pyrimidin-2-yl)-3-methylbutyramide (14). Yield 48%;
white solid; mp 134-135 °C; ^1H NMR δ (CDCl_3): 8.27 (br s, 1H, *NH*), 8.15-8.07
(m, 4H, ar),
30 7.79 (s, 1H, pyrimidinyl-*H*), 7.55-7.47 (m, 6H, ar), 2.87 (d, 2H, $J = 7.30$, CH_2),

2.40-2.26 (m, 1H, CH), 1.06 (d, 6H, J = 6.94, 2x CH₃)ppm. ¹³C NMR δ (CDCl₃): 173.1, 166.0, 157.8, 136.6, 131.1, 128.9, 127.2, 107.4, 46.3, 25.3, 22.6ppm.

MS: 345.9, 367.6 Da. Anal. (C₂₁H₂₁N₃O_{0.35}H₂O) C, H, N.

- 5 **N-(4,6-Diphenyl-pyrimidin-2-yl)-2-ethyl-butyramide (15).** Yield 22%; white solid;

mp 120-121 °C; ¹H NMR δ (CDCl₃): 8.18-8.13 (m, 4H, ar), 8.11 (br s, 1H, NH), 7.84 (s, 1H, pyrimidinyl-H), 7.56-7.51 (m, 6H, ar), 2.97 (m, 1H, CH(CH₂CH₃)₂), 1.94-1.59 (m, 4H, CH(CH₂CH₃)₂), 1.02 (t, 6H, J = 7.30 Hz, CH(CH₂CH₃)₂)ppm.

- 10 ¹³C NMR δ (CDCl₃): 166.0, 157.7, 136.6, 130.9, 128.8, 127.1, 121.6, 107.6, 50.1, 24.9, 11.8ppm. MS (ES⁺): 324.86, 690.57 Da. Anal. (C₂₂H₂₃N₃O) C, H, N.

Cyclohexanecarboxylic acid-(4,6-diphenyl-pyrimidin-2-yl)-amide (16).

Yield 26%; white solid; mp 172 °C; ¹H NMR δ (CDCl₃): 8.11-8.19 (m, 4H, ar),

- 15 7.83 (s, 1H, pyrimidinyl-H), 7.50-7.57 (m, 6H, ar), 0.83-2.10 (m, 11H, CH₂ + CH)ppm. ¹³C NMR δ (CDCl₃): 166.1, 157.8, 136.6, 131.0, 128.8, 127.2, 022.7, 121.7, 107.5, 44.9, 29.1, 25.6ppm. MS: 357.8 Da. Anal. (C₂₃H₂₃N₃O.0.05EtOH) C, H, N.

- 20 **Cyclopentane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide (17).**

Yield 98%; white solid; mp 145-146 °C; ¹H NMR δ (CDCl₃): 8.16-8.11 (m, 4H, ar),

7.82 (s, 1H, pyrimidinyl-H), 7.55-7.51 (m, 6H, ar), 2.04-1.65 (m, 9H,

cyclopentane)ppm. ¹³C NMR δ (CDCl₃): 176.2, 165.9, 157.8, 131.0, 128.8, 127.1,

- 25 107.4, 45.7, 30.1, 26.0ppm. MS: 344.2 Da. Anal. (C₂₂H₂₁N₃O.0.13H₂O) C, H, N.

Table 1 – Elemental Analysis

Compound No.	Molecular formula	Elemental Analysis		
		C%	H%	N%
9	C ₂₃ H ₁₇ N ₃ O Calc.	78.61	4.88	11.96
	Found	78.10	4.88	12.58
10	C ₁₉ H ₁₇ N ₃ O. 0.2H ₂ O	74.30	5.72	13.68
		74.31	6.11	13.79
11		HRMS: 318.16 Da		
12	C ₂₁ H ₂₁ N ₃ O. 0.1H ₂ O	75.70	6.35	12.61
		75.30	6.38	12.77
13	C ₂₀ H ₁₉ N ₃ O	75.69	6.03	13.24
		75.33	6.15	13.43
14	C ₂₁ H ₂₁ N ₃ O.0.35H ₂ O	74.69	6.27	12.44
		74.71	6.27	12.63
15	C ₂₂ H ₂₃ N ₃ O	76.49	6.71	12.16
		76.21	6.99	12.35
16	C ₂₃ H ₂₃ N ₃ O.0.05EtO	76.34	6.41	11.61
	H	76.41	6.40	11.72
17	C ₂₂ H ₂₁ N ₃ O.0.1H ₂ O	76.40	6.20	12.15
		76.37	6.57	12.49

BIOLOGY

A primary function of certain cell surface receptors is to recognise appropriate ligands. Accordingly, we performed radioligand binding studies to establish the degree to which the compound binds to the receptor.

5

Radioligand Binding Studies [³H]DPCPX was purchased from Amersham. All compounds made were tested in radioligand binding assays to determine their affinities at the human adenosine A₁ receptor. The affinities at the A₁ receptors were determined on CHO cells expressing the human receptors, using [³H]DPCPX as the radioligand according to a previously described method.⁸

10

Data Analysis Competition binding data were fit to a single-site binding model and plotted using the software package Prism (Graph Pad, San Diego, CA, USA). The Cheng-Prusoff equation $K_i = IC_{50}/(1+[I]/K_d)$ was used to calculate K_i values, where K_i is the affinity constant for the competing ligand, [I] is the concentration of the free radioligand, and K_d is the affinity constant for the radioligand.

15

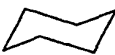

20 Structure Activity Relationships

In Table 2 results of the radioligand binding assays at the A₁ receptor are displayed, the substituents are defined hereinabove and below with reference to the compound of general formula (II). The reported literature focuses generally on bi-, and tri-cyclic heterocycles as the core structure about which substituents are varied. This monocyclic core with the 2,4,6-trisubstitution pattern has surprising efficacy at the adenosine A₁ receptor, as can be seen in Table 2. The compounds shown in Table 2 were also tested at the adenosine A_{2A} and A₃ receptors and were shown to be generally selective for the adenosine A₁ receptor.

25

30

Table 2 – Radioligand Binding Assay

comp	R	A ₁ ^a
9	Ph	309±73
10	CH ₂ CH ₃	46.4±2.5
11	(CH ₂) ₂ CH ₃	3.70±1.94
12	(CH ₂) ₃ CH ₃	27.6±10.3
13	CH(CH ₃) ₂	8.87±4.2
14	CH ₂ CH(CH ₃) ₂	25.1±6.6
15	CH(CH ₂ CH ₃) ₂	27.1±5.7
16		119±42
17		11.4±2.4

^aDisplacement of specific [³H]DPCPX binding in CHO cells expressing human adenosine A₁ receptors. K_i (nM) ± SEM (n = 3).

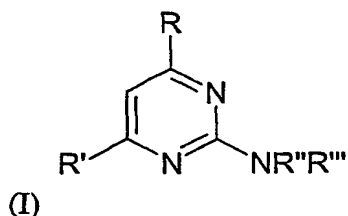
LIST OF REFERENCES

1. Fredholm, B. B.; IJzerman, A. P.; Jacobson, K. A.; Klotz, K.-N.; Linden, J. International Union of Pharmacology. XXV. Nomenclature and
5 Classification of Adenosine Receptors. *Pharmacological Reviews* 2001, 53, 527-552.
- 2) Van Galen, P. J. M.; Nissen, P.; van Wijngaarden, I.; IJzerman, A. P.; Soudijn, W. 1H-Imidazo[4,5-c]quinolin-4-amines: Novel Non-Xanthine Adenosine Antagonists. *Journal of Medicinal Chemistry* 1991, 34, 1202-1206.
- 10 3) Sarges, R.; Howard, H. R.; Browne, R. G.; Lebel, L. A.; Seymour, P. A. et al. 4-Amino[1,24]triazolo[4,3-a]quinoxalines. A Novel Class of Potent Adenosine Receptor Antagonists and Potential Rapid-Onset Antidepressants. *Journal of Medicinal Chemistry* 1990, 33, 2240-2254.
- 4) Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Pineda de las Infantas y
15 Villatoro, M. J.; Zocchi, C. et al. Pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine Derivatives: Potent and Selective A_{2A} Adenosine Antagonists. *Journal of Medicinal Chemistry* 1996, 39, 1164-1171.
- 5) Baraldi, P. G.; Cacciari, B.; Romagnoli, R.; Spalluto, G.; Moro, S. et al. Pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine Derivatives as Highly Potent and
20 Selective Human A₃ Adenosine Receptor Antagonists: Influence of the Chain at the N8 Pyrazole Nitrogen. *Journal of Medicinal Chemistry* 2000, 43, 4768-4780.
- 6) Hess, S.; Müller, C. E.; Frobenius, W.; Reith, U.; Klotz, K.-N. et al. 7-Deazaadenines Bearing Polar Substituents: Structure-Activity Relationships
25 of New A₁ and A₃ Adenosine Receptor Antagonists. *Journal of Medicinal Chemistry* 2000, 43, 4636-4646.
- 7) Al-Hajjar, F. H.; Sabri, S. S. Reaction of Beta-Unsaturated Ketones with Guanidine. Substituent Effects on the Protonation Constants of 2-Amino-4,6-diarylpurines. *Journal of Heterocyclic Chemistry* 1982, 19, 1087-1092.

- 8) Priego, E. M.; von Frijtag Drabbe Künzel, J. K.; IJzerman, A. P.; Camarosa, M.-J.; Pérez-Pérez, M.-J. Pyrido[2,1-f]purine-2,4-dione Derivatives as a Novel Class of Highly Potent A₃ Adenosine Receptor Antagonists. *Journal of Medicinal Chemistry* **2002**, *45*, 3337-3344.

Claims

1. A compound having the structure of general formula (I):

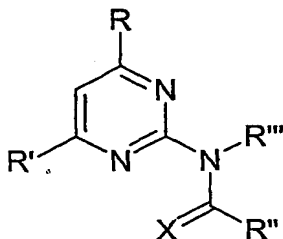


or a salt thereof,
wherein

- 5 R represents hydrogen (except when R'=H), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) (CH₂)_n-aryl;
R' represents hydrogen (except when R=H), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) (CH₂)_n-aryl;
R'' represents hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl,
10 (substituted) alkenyl, (substituted) alkynyl, or (substituted) (CH₂)_n-aryl;
R''' represents hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) (CH₂)_n-aryl;
R'' and R''' can also together form a substituted or unsubstituted heterocyclic ring or heterocyclic rings; and n is a number in the range of from 0 to 10.

15

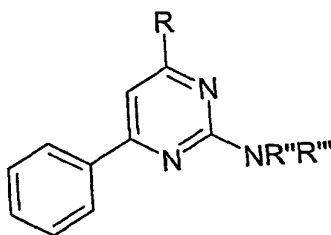
2. The compound according to claim 1, having the structure:



or a salt thereof,
wherein

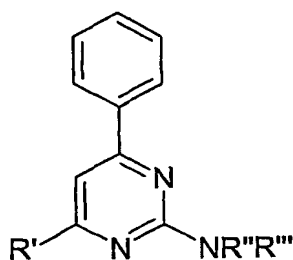
- R represents hydrogen (except when $R'=H$), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $(CH_2)_n$ -aryl;
 R' represents hydrogen (except when $R=H$), (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $(CH_2)_n$ -aryl;
 5 R'' represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $(CH_2)_n$ -aryl;
 R''' represents hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $(CH_2)_n$ -aryl;
 X represents oxygen, sulfur or selenium; and n is a number in the range of
 10 from 0 to 10.

3. A compound according to claim 1, having the structure:



- or a salt thereof,
 15 wherein
 R represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl;
 R'' represents hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl;
 20 R''' represents hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl; and
 n is a number in the range of from 0 to 10.

4. A compound according to claim 1, having the structure:



or a salt thereof,

wherein

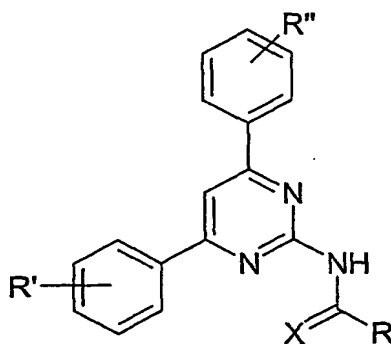
R' represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted)
5 alkynyl, or (substituted) $-(CH_2)_n$ -aryl;

R'' represents hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl,
(substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl;

R''' represents hydrogen, acyl, thio-acyl, seleno-acyl, (substituted) alkyl,
(substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl; and

10 n is a number in the range of from 0 to 10.

5. The compound according to claim 1 or 2, having the structure:



or a salt thereof,

15 wherein

R represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted)
alkynyl, or (substituted) $(CH_2)_n$ -aryl;

R' represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) $(CH_2)_n$ -aryl, alkoxy, thioalkyl, halo, NR_1R_2 , NR_3COR_4 , or $NR_5CONR_6R_7$;

- 5 R'' represents hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, (substituted) $(CH_2)_n$ -aryl, alkoxy, thioalkyl, halo, NR_1R_2 , NR_3COR_4 , or $NR_5CONR_6R_7$; wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are independently selected from hydrogen, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $(CH_2)_n$ -aryl; and when R_1 and R_2 are in a NR_1R_2 group, or when R_6 and R_7 are in a NR_6R_7 then R_1 and R_2 may be linked to form a heterocyclic group, and R_6 and R_7 may be linked to form a heterocyclic group; X represents oxygen, sulfur or selenium; and
- 10 n is a number in the range of from 0 to 10.

6. A compound according to any one of claims 1-5, which compound is
- 15 chosen from the group consisting of N- (4,6-diphenyl-pyrimidin-2-yl)-benzamide, N- (4,6-diphenyl-pyrimidin-2-yl)-formamide, N- (4,6-diphenyl-pyrimidin-2-yl)-propionamide, N- (4,6-diphenyl-pyrimidin-2-yl)-butyramide, pentanoic acid (4,6-diphenyl-pyrimidin-2-yl)-amide, N- (4,6-diphenyl-pyrimidin-2-yl)-isobutyramide, N- (4,6-diphenyl-pyrimidin-2-yl)-2,2-dimethyl-
- 20 propionamide, N- (4,6-diphenyl-pyrimidin-2-yl)-3-methylbutyramide, N- (4,6-diphenyl-pyrimidin-2-yl)-2-ethyl-butyramide, cyclopropane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide, cyclobutane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide, cyclopentane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide, cyclohexanecarboxylic acid-(4,6-diphenyl-pyrimidin-2-yl)-amide, or
- 25 a salt thereof.

7. A compound according to claim 6, wherein the compound is chosen from the group consisting of N-(4,6-diphenyl-pyrimidin-2-yl)-formamide, N-(4,6-diphenyl-pyrimidin-2-yl)-propionamide, N-(4,6-diphenyl-pyrimidin-2-yl)-butyramide, pentanoic acid (4,6-diphenyl-pyrimidin-2-yl)-amide, N-(4,6-
- 30

diphenyl-pyrimidin-2-yl)-isobutyramide, N-(4,6-diphenyl-pyrimidin-2-yl)-2,2-dimethyl-propionamide, N-(4,6-diphenyl-pyrimidin-2-yl)-3-methylbutyramide, N-(4,6-diphenyl-pyrimidin-2-yl)-2-ethyl-butyramide, cyclopentane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide.

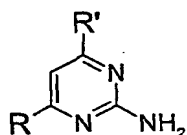
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8. A compound according to claim 7, which compound comprises N-(4,6-diphenyl-pyrimidin-2-yl)-formamide, N-(4,6-diphenyl-pyrimidin-2-yl)-butyramide, N-(4,6-diphenyl-pyrimidin-2-yl)-3-methylbutyramide, or cyclopentane carboxylic acid (4,6-diphenyl-pyrimidin-2-yl)-amide).

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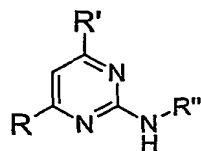
9. A process for preparing a compound according to any one of claims 1-8, which process comprises the steps of:

(a) reacting a compound having the structure $\text{RCOCHCHR}'$ with guanidine, or a salt thereof, to form a product having the structure



15 wherein R represents hydrogen (except when $R' = \text{H}$), (substituted) alkyl, substituted alkenyl, (substituted) alkynyl or (substituted) $-(\text{CH}_2)_n\text{-aryl}$; R' represents hydrogen (except when $R = \text{H}$), (substituted) alkyl, substituted alkenyl, (substituted) alkynyl or (substituted) $-(\text{CH}_2)_n\text{-aryl}$; and n is a number in the range of from 0 to 10;

20 (b) reacting the product formed in step (a) with a compound having the structure of $R''\text{aldehyde}$, $R''\text{halide}$ or $R''\text{carboxylic acid}$ or a derivative thereof,

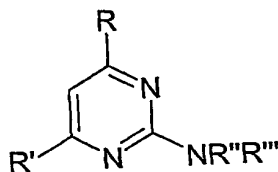


to form a product having the structure

wherein R" represents (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl or (substituted) $-(CH_2)_n$ -aryl, wherein n has the meaning as defined herein before;

and

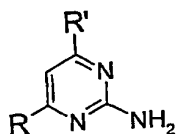
- 5 (c) reacting the product formed in step (b) with a compound having the structure of R"aldehyde, R"halide or R"carboxylic acid or a derivative thereof, to form a product having the structure



- 10 wherein R''' represents acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl or (substituted) $-(CH_2)_n$ -aryl, and wherein n has the meaning as defined hereinbefore.

10. A process for preparing a compound according to any one of claims 1-8,
15 which process comprises the steps of:

- (a) reacting a compound having the structure $RCOCHCHR'$ with guanidine, or a salt thereof, to form a product having the structure

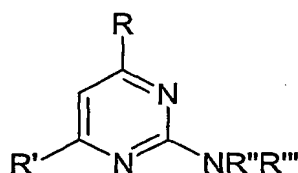


20

wherein R represents hydrogen (except when $R' = H$), (substituted) alkyl, substituted) alkenyl, (substituted) alkynyl or (substituted) $-(CH_2)_n$ -aryl; R'

represents hydrogen (except when $R = H$), (substituted) alkyl, substituted alkenyl, (substituted) alkynyl or (substituted) $-(CH_2)_n$ -aryl; and wherein n is a number ranging of from 0 to 10; ;

- (b) reacting the product formed in step (a) with a compound having the structure of R'' aldehyde, R'' halide or R'' carboxylic acid or a derivative thereof, to form a product having the structure



- R'' represents acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl or (substituted) $-(CH_2)_n$ -aryl; R''' represents acyl, (substituted) alkyl, (substituted) alkenyl, (substituted) alkynyl, or (substituted) $-(CH_2)_n$ -aryl; and wherein n has the meaning as defined hereinbefore.

11. A pharmaceutical composition comprising as active ingredient one or more compounds according to any one of claims 1-8.
12. The use of a compound according to any one of claims 1-8 for treating and/or preventing a disorder in which the adenosine receptors are involved.
13. The use of a compound according to any one of claims 1-8 for treating and/or preventing a disorder in which the adenosine receptors are blocked.
14. The use of a compound according to any one of claims 1-8 for the manufacture of a medicament for the treatment and/or prevention of a disorder in which the adenosine receptors are involved.

15. The use of a compound according to any one of claims 1-8 for the manufacture of a medicament for the treatment and/or prevention of a disorder in which the adenosine receptors are blocked.

5 16. The use according to claims 12 to 15, wherein the disorder is chosen from the group of diseases consisting of amongst others cardiovascular, neurological, immunological disorders, cancers and infection conditions.

10 17. The use according to claims 12 to 16, wherein the disorder is chosen from the group of diseases consisting of kidney, heart and central nervous system (CNS) afflictions.

15 18. A method for treating and/or preventing a disorder in which the interaction with the adenosine receptors is beneficial, which method comprises administering to a subject in need of such treatment an effective dose of a pharmaceutical composition according to claim 11.

20 19. The method according to claim 18, wherein the disorder is chosen from the group of diseases consisting of amongst others cardiovascular, neurological, immunological disorders, cancers and infection conditions.

20. The method according to claim 19, wherein the disorder is chosen from the group of diseases consisting of kidney, heart and central nervous system (CNS) afflictions.

INTERNATIONAL SEARCH REPORT

PCT/NL2004/000683

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/42 A61K31/505 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 586 441 B2 (BORRONI EDILIO MAURIZIO ET AL) 1 July 2003 (2003-07-01) column 1, line 14 - column 3, line 45	5-20
X	EP 0 767 170 A (TAIHO PHARMACEUTICAL CO LTD) 9 April 1997 (1997-04-09) claim 1; compound 32	5, 11
X	FAROUK H. AL-HAJJAR ET AL: "Reaction of alpha,beta-unsaturated ketones with guanidine. Substituent effects on the protonation constants of 2-amino-4,6-diarylpyrimidines." J. HETEROCYCLIC CHEM., vol. 19, 1982, pages 1087-1092, XP002311657 Scheme 1 : compound IV	5



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

21 December 2004

Date of mailing of the international search report

05/01/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

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PCT/NL2004/000683

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim No.
Category *	Citation of document, with indication, where appropriate, of the relevant passages	
A	WO 03/035639 A (KABASAWA YASUHIRO ; ASANO OSAMU (JP); UEDA MASATO (JP); EISAI CO LTD () 1 May 2003 (2003-05-01) paragraph '0008! - paragraph '0009!; claim 1	5-20
P,A	& EP 1 439 175 A (EISAI CO LTD) 21 July 2004 (2004-07-21)	
X	DATABASE CROSSIFRE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002311658 Database accession no. BRN: 9668908 abstract & EGYPT. J. CHEM., vol. 45, no. 5, 2002, pages 895-904,	5
X	DATABASE CROSSIFRE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002311659 Database accession no. BRN: 5102262 abstract & TETRAHEDRON, vol. 45, no. 6, 1989, pages 1783-1792,	1
X	DATABASE CROSSIFRE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002311660 Database accession no. BRN: 129405 abstract & CHEM. BER., vol. 96, 1963, pages 1505-1514,	1
X	DATABASE CROSSIFRE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002311661 Database accession no. BRN: 745547 abstract & CHEM. HETEROCYCL. COMPD., vol. 11, 1975, pages 1322-1324,	1

INTERNATIONAL SEARCH REPORT

PCT/NL2004/000683

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6586441	B2	04-10-2001	AU 5464301 A	03-09-2001
			BR 0108611 A	06-05-2003
			CA 2398274 A1	30-08-2001
			CN 1438890 T	27-08-2003
			CZ 20023199 A3	14-05-2003
			WO 0162233 A2	30-08-2001
			EP 1261327 A2	04-12-2002
			HU 0300029 A2	28-05-2003
			JP 2003523380 T	05-08-2003
			MX PA02008240 A	29-11-2002
			NO 20024006 A	22-08-2002
			NZ 520241 A	28-05-2004
			US 2001027196 A1	04-10-2001
			ZA 200206077 A	30-10-2003
EP 0767170	A	09-04-1997	AT 226574 T	15-11-2002
			AU 692090 B2	28-05-1998
			AU 5289296 A	30-10-1996
			CA 2190973 A1	17-10-1996
			DE 69624437 D1	28-11-2002
			DE 69624437 T2	07-08-2003
			EP 0767170 A1	09-04-1997
			KR 275300 B1	15-12-2000
			NO 965334 A	12-02-1997
			US 5786355 A	28-07-1998
			HU 9603433 A2	28-08-1997
			WO 9632384 A1	17-10-1996
			JP 3145410 B2	12-03-2001
WO 03035639	A	01-05-2003	BR 0213455 A	19-10-2004
			CA 2463284 A1	01-05-2003
			EP 1439175 A1	21-07-2004
			WO 03035639 A1	01-05-2003
EP 1439175	A	21-07-2004	BR 0213455 A	19-10-2004
			CA 2463284 A1	01-05-2003
			EP 1439175 A1	21-07-2004
			WO 03035639 A1	01-05-2003

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